Prevalence of familial hypercholesterolaemia in three rural South African communities

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Summary

The prevalence of familial hypercholesterolaemia (FH) was estimated in three predominantly Afrikaner communities in the south-western Cape. Young hypercholesterolaemics (N = 136) identified during the Coronary Risk Factor Study (CORIS) and their first-degree relatives were invited to attend a follow-up study of their blood lipids (total and high-density lipoprotein cholesterol and triglyceride values) 6 months after the CORIS baseline study. Of the 62 index cases who fulfilled the qualifying conditions, 7 were classified as suffering from FH. This ratio of 7 FH cases out of 62 index cases represents a prevalence of 1:87 in the study population, which is considerably higher than the 1:500 found elsewhere in the world. For several reasons 1:87 may be seen as an underestimate.

The mean serum cholesterol level in the 7 FH cases was 10.08 mmol/l. Fasting triglyceride values indicated that type Ia was the most frequent hyperlipoproteinaemia. The mean percentage of high-density lipoprotein: total cholesterol in the FH cases was also considerably below either the same age group in the CORIS population or the index cases not classified as FH.

Explanations for the excessively high coronary heart disease (CHD) mortality rate among white South Africans may result from any of these possibilities. In the RSA, with its high CHD mortality and morbidity rates, surprisingly little is known about the prevalence of the genetic component of hypercholesterolaemia. The excessive CHD mortality rate among younger Afrikaans-speaking South Africans may point to an important genetic component. Familial hypercholesterolaemia (FH) either in the homozygotic or in the heterozygotic form is unusually prevalent in white South Africans in the Witwatersrand area. In that area, FH appears to cluster among members of a particular Afrikaans-speaking religious denomination, who may to some extent represent a genetic isolate. In the three-community Coronary Risk Factor Study (CORIS) in the south-western Cape almost a third of the population exceeded the conventional cut-off point of 6.46 mmol/l for hypercholesterolaemia. The possibility that FH makes up a substantial proportion of the hypercholesterolaemias in the predominantly Afrikaans-speaking CORIS population needed investigation. A group of young hypercholesterolaemic index cases and their families, identified during the CORIS baseline study, were therefore re-examined 6 months after the original study. An extensive community survey, in contrast with registrations at clinics in earlier studies, served as the point of departure of the present study. This report describes the determination of the prevalence of FH in these three rural communities.

Subjects and methods

The CORIS study was carried out in three south-western Cape communities early in 1979. It was shown that hypercholesterolaemia (≥ 6.46 mmol/l) prevailed in 30.1% of the men and 34.4% of the women. The study population consisted of the whites aged 15 - 64 years residing within the magisterial districts of Swellendam, Riversdale and Robertson. Non-fasting blood samples were taken from the 7 188 respondents as part of a cross-sectional coronary risk factor study and analysed manually on the same day for serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels by means of the Boehringer CHOD-PAP enzymatic method after dextran sulphate-magnesium chloride precipitation of Apo B-containing lipoproteins. Reference standards (Ortho Diagnostics and Boehringer Precilip) were included in each batch.
The frequency distribution curves of the serum cholesterol values were markedly skewed to the right. FH cases were usually located at the top end of such distribution curves. For the purpose of this study, respondents aged 16 - 25 years were used to establish the prevalence of FH, because younger individuals had had the least exposure to environmental factors which could induce hypercholesterolaemia. Men and women in this age category who were found to exceed the 90th percentile for VLDL-LDL cholesterol (= total cholesterol minus HDL-C) were used as index cases for the FH study. This would tend to exclude subjects with high TC values owing to markedly raised HDL-C levels.

These index cases and their first-degree relatives were re-examined 6 months later by determining fasting serum TC, HDL-C and triglyceride levels. Fasting triglyceride levels at a cut-off level of 1.7 mmol/l were used to phenotype the positively identified FH cases. Methods similar to those described earlier were used to analyse for cholesterol and HDL-C levels. Serum triglyceride levels were analysed using the Boehringer Mannheim enzymatic method.

Because the mean cholesterol concentration of index cases and their families upon re-examination were approximately 14% lower than in the original study, questionnaires were mailed to them. The object of the questionnaire was to obtain information on changes in lifestyle which could help to explain the decrease in serum cholesterol values.

A separate study on the association between diet and blood lipids was conducted at the same time as the FH follow-up study in the same population, but on 25 - 34-year-old men and women. Of the study groups in the diet study was selected on the basis of its low TC values (below the 15th percentile) during the CORIS baseline study. A mean decrease in TC of 7.8% was observed in this group between the original baseline and the follow-up study 6 months later. Assuming a similar decrease in TC to other age groups, this decrease of 7.8% at the lower end of the TC distribution was therefore considered as the minimum change in TC in the whole population as a result of interim intervention effects. The effect of regression to the mean is excluded from the 7.8% intervention effect because it operates in the opposite direction at the lower end of the TC distribution. In addition to the uncorrected TC values, a second set of corrected TC values was therefore obtained by increasing the TC values of the FH follow-up study by 7.8% to compensate for the intervention effects.

Two prevalence rates of FH were calculated, based on the corrected as well as on the corrected follow-up TC values. The following criteria were used for identification of FH in the present study: (i) TC of the index case ≥ 95th percentile in both sampling periods; and (ii) at least 1 first-degree relative with TC ≥ 95th percentile for the relevant age and sex category in the follow-up study.

Only families represented by two observations on the index person and at least 2 first-degree relatives available at the follow-up study were considered for the classification of FH.

**Results**

Of the 1335 respondents in the 16 - 25 year age group examined during the CORIS baseline study, 136 equalled or exceeded the 90th percentile for the age and sex specific total minus HDL-C. These 136 individuals formed the index cases for the FH study (Fig. 1). Of the 136 subjects 10 did not report for re-examination after 6 months. In 38 subjects the number of available family members was inadequate and in 26 neither the index case nor the family members were available during the follow-up study. These 74 families therefore did not qualify for FH classification. The balance of 62 families were considered for FH classification of the index case because in these families at least 2 first-degree relatives were studied at follow-up and the index case was studied on both occasions.

Using our identification criteria, 7 out of the 62 available subjects were positively identified as having FH. On this basis the calculated prevalence of FH was 1:87 in the study population (Fig. 1); this figure represents the most conservative estimate.

Should the TC values obtained during the second sampling 6 months later be adjusted upward by 7.8%, to correct for the apparent population shift due to intervention effects during the interval between the two sampling sessions but excluding regression to the mean, then 13 of the 62 cases were positive. This figure corresponds to a FH prevalence of 1:47 in the study population (Fig. 1). The CORIS baseline TC distribution of the 62 qualifying index cases is illustrated in Fig. 2, which shows that FH cases tend to concentrate in the top end of the distribution.

**Fig. 2. TC distribution of the 62 index cases.**

Fasting serum triglyceride values in only 1 of the group of 7 and 2 of the group of 13 positive FH cases exceeded 1.7 mmol/l. Fredrickson's type IIA was therefore the most frequent phenotype found in FH cases.

Approximately half the mailed questionnaires enquiring about lifestyle changes since the CORIS study 6 months earlier were returned. From these completed questionnaires it appears that the CORIS study itself, as well as the individual results subsequently mailed to respondents, had an intervention effect. Briefly, these questionnaires showed that 74% of the respondents changed their diet, 28% became physically more active and 11% of the smokers stopped the habit. It also showed that none of the respondents was on medication for hypercholesterolaemia.

In Table 1 the mean blood lipid values of the FH and normal index cases are given. The mean TC in the 7 FH subjects — 10.08 mmol/l — is considerably higher than the 6.6 mmol/l of the 55 normal index cases. The mean HDL concentration was 1.21 mmol/l and 1.14 mmol/l in the 7 FH and 55 normal index cases respectively. Expressed as a percentage of TC, the mean % HDL/TC in the 7 FH subjects was 12% and in the 55 normal index cases 17%. Serum triglyceride values were approximately similar in the two groups.
Discussion

From the present FH study as well as from previous studies undertaken elsewhere in the RSA, it appears that the prevalence of FH is consistently found to be remarkably high, irrespective of the approach used in the different studies. In our community-based study two prevalence estimates were derived from the data. A conservative estimate indicated that 1:87 of the study population suffered from FH, not taking a shift in the lipid values during the study period into consideration. After correcting statistically for the intervention component of the shift, the prevalence of FH increased to an even more alarming figure of 1:47.

Estimates of the prevalence of FH elsewhere in the RSA was derived from data obtained from registrations at clinics. These estimates were in the order of 1 in 100, which may also be accepted as conservative in view of the incomplete FH population registration at any single clinic. Elsewhere in the world heterozygous FH occurs in the general population at a frequency of about 1 in 500. Compared with the latter figure heterozygous FH appears to be between 5 and 10 times more prevalent in the South African study population.

Although neither LDL receptor analyses nor a selective clinical examination for expression of clinical signs of FH were included in our study, the segregation of the allele within families was used as one of the determining identification criteria. In the absence of extensive laboratory tests and clinical examinations, the distribution of TC in individuals and within families may serve as a robust indicator of the prevalence of FH in large population samples. Leonard et al. also succeeded in diagnosing FH in a hospital sample of children with at least 1 first-degree relative with presumed FH. They measured serum TC levels and by using a maximum likelihood technique, fitted two overlapping curves, thereby misdiagnosing 4.25% of cases. However, Kwitterovich et al. warned against the use of TC as a test for type IIa hyperlipoproteinaemia in a general population in view of the large number of false-positive and false-negative results obtained in this way. These uncertainties may largely be overcome with the use of LDL receptor studies in index cases.

Our estimate of 1 case of FH in 87 in the study population should, for several reasons, be seen as a conservative estimate. A study design which includes repeat observations on extreme portions of the population distribution — in this case the highest decile of the TC minus HDL-C distribution — inevitably introduces regression to the mean, resulting in a lower mean at follow-up and therefore fewer positive cases. In practice, regression to the mean operated in combination with the intervention effects at follow-up, leading to a net lowering in blood lipids and therefore also to the conservative estimate of the prevalence of FH.

In a cross-sectional study such as the CORIS baseline and the follow-up FH studies, the design introduces a potential bias against the purpose of the investigation by virtue of the probability that parents or other family members of index cases may have died as a result of the disease under investigation. These families had a more limited chance of being included for consideration and classification and therefore may have indirectly contributed to an underestimation of the prevalence of FH. The mean number of family members of the 7 FH subjects was 4.43 and of the normal index cases 3.36.

There is hardly any reason to believe that the prevalence of FH among the 74 index cases who did not fulfill the classification criteria, in other words those who were not studied twice or those with insufficient family members, was different from those 62 index cases considered for classification. Since heterozygous FH is largely asymptomatic, all index cases were informed in the same way about their elevated TC values. Since they were not aware of their FH status, selective volunteering was unlikely. It is, however, possible that families of a history of CHD could have attended more faithfully.

On the other hand, as mentioned earlier, family fatalities due to CHD would tend to disqualify rather than qualify an index person for classification as FH. Similarly, the investigators invited all the index subjects and their families equally emphatically to attend the follow-up examination. Therefore there was no selective search for certain individuals. The mean CORIS baseline TC of 7.0 mmol/l of the group who qualified for FH classification (N = 62) was also not significantly different from the mean of 6.74 mmol/l of those who did not qualify (N = 74). The HDL-C and % HDL:TC values for these two groups were also virtually similar. It is therefore doubtful that the relatively small number of index cases qualifying for FH classification (62 out of 136) influenced the final outcome. The probability that the outcome was due to chance is also low, particularly in view of the good agreement of our results with previous research on different study populations elsewhere in the RSA.

When age and sex specific reference values for the 95th percentile of North Americans, as obtained from the Lipid Research Clinics Program (LRC), are used and our FH classification criteria applied, then 23 of the possible 62 subjects were classified as having FH. This figure suggests the extremely high FH prevalence of 1:27 in our study population. Laboratory error is an unlikely explanation for this high estimate of FH prevalence because our laboratory analysis for TC was standardized against the LRC with a 10% underestimation on our side.

The mean CORIS TC value of 10.08 mmol/l of the 7 heterozygous FH subjects in our study is higher than that of 5 studies on heterozygous FH cited by Goldstein and Brown. In this series of studies the mean TC ranged from 8.79 to 9.46 mmol/l. This higher TC mean value serves as another indicator of the strict classification criteria used in our study and hence of the conservative results. These 7 FH cases occurred at the top of the TC distribution (Fig. 1), all of them exceeding 7.75 mmol/l during the CORIS baseline study. It should also be noted that some subjects who exceeded the 7.75 mmol/l level were not classified as FH because none of their available family members exceeded their age and sex specific 95th percentile levels. The mean TC of the 55 index cases not classified as FH was 6.64 mmol/l, which was considerably lower than the mean of the 7 FH subjects and, as expected, considerably higher than the mean CORIS population values of 4.55 mmol/l for men and 4.96 mmol/l for women of the same age.

The mean HDL level of 1.21 mmol/l of the 7 FH subjects, which fell between the 1.14 mmol/l for CORIS men and 1.35

| TABLE I. MEAN BLOOD VALUES OF FH AND NORMAL INDEX CASES (± SD) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | N               | TC (mmol/l)     | HDL (mmol/l)    | % HDL: TC       |
| FH               | 7               | 10.08 ± 2.09    | 1.21 ± 0.28     | 12.0 ± 3.3      | 1.28 ± 0.57    |
| Normal index cases | 55             | 6.46 ± 0.67     | 1.14 ± 0.34     | 17.2 ± 4.3      | 1.30 ± 0.73    |
*Measured at follow-up study.
mmol/l for CORIS women of the same age, was slightly higher than that of the 55 normal index cases (Table I). This was most probably due to the higher proportion of women (5 out of 7) among the FH cases, whereas among the 55 normal index cases only 25 were women. However, the mean % HDL:TC level of 12% in the FH group was markedly lower than the mean of 17% observed in the normal index cases. Both these values were considerably lower than the means of approximately 25% and 27% for men and women of similar age in the CORIS population from which the FH subjects were identified. It therefore appears that the mean % HDL:TC level of the 55 normal index cases was only two-thirds as high as the mean value of the population from which the index cases were drawn. The mean % HDL:TC level of the 7 FH subjects, in turn, was 70% of the mean of the normal index cases and less than half that of the CORIS population.

In summary, the present community-based study provides evidence for the excessive prevalence of FH in the southwestern Cape, as in the Witwatersrand area. The majority of our FH subjects were Type IIa hyperlipoproteinemia characterized, as elsewhere, by high TC, normal triglyceride and low % HDL:TC values.

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REFERENCES


Disease patterns in a rural black population

P. A. REEVE, M. J. FALKNER

Summary

Epidemiological information concerning disease patterns among blacks in southern Africa is scanty and a plea has been made for greater research. Between September 1968 and January 1970, patients admitted to the medical wards of Jane Furse Hospital in Lebowa were studied; 14 years later the study was repeated and the results compared. The increasing incidence of asthma, hypertension and diabetes, well recognized in urban blacks, seems to be reflected in the rural setting of Jane Furse Hospital. Tuberculosis remains a common problem and a cause for concern.

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Epidemiological information concerning disease patterns among blacks in southern Africa is lacking, and Seftel has made a plea for more research into the prevalence of disease. The difficulties involved in such studies in black communities has meant that most information is based on hospital experience. Between September 1968 and January 1970, Edginton et al. studied 485 female and 53 male patients admitted to the medical wards of Jane Furse Memorial Hospital, Lebowa. It was decided 14 years later to record the final diagnosis for all patients admitted to the medical wards of the same hospital. While realizing the limitations of such a study, we feel that the results are worth presenting, both as an indication of the problems in this area and to point out some apparent similarities to and differences from the patterns of 14 years ago.

Patients and methods

Jane Furse Memorial Hospital is the regional hospital for southern Lebowa, serving, with 3 other subsidiary hospitals, a population of about 400 000. The majority of the patients belong to the Transvaal Sotho group.

All patients admitted to the adult medical wards between 1 November 1982 and 31 October 1983 are included. Patients suspected of having typhoid, meningitis, infectious hepatitis, tetanus and infectious diarrhoea were admitted to separate wards.